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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/562,081	VUOLTEENAHO ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) *28-37 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *23 December 2005, the 3 April 2006 and the 8 November 2006*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Restriction Requirement:

Applicants' election, without traverse of Group I, claims 1-28 and 38, drawn to an agent which comprises an ANP and a BNP, a polynucleotide encoding said agent, an expression vector comprising said polynucleotide, a host cell comprising said polynucleotide, and a method for producing said agent recombinantly and *in vitro* method of determining activation or inactivation of ANP and BNP hormonal system on 10 July 2008 is acknowledged. In response to requirement for species election, applicant elected: SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:12 and SEQ ID NO:14,.

Upon further consideration, the requirement for species election #3, to elect a single species of agent as recited in claims 10 and 19, identified by SEQ ID NO: as recited in claim 20 (SEQ ID NOs 13-20) is rescinded.

In the requirement for restriction of 13 June 2008, the Examiner erroneously included claim 28 in Group I. Claim 28 is drawn to a process for producing a polypeptide by chemical synthesis, and is thus a second method of manufacture and therefore belongs in a separate group. MPEP 1850 (d) states "If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c)." The Examiner regrets any confusion due to the error.

Claims 1-38, and 40-44 are pending in the instant application. Claims 28-37 and 40-44 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-27 and 38 are under consideration to the extent they read on the elected invention.

Priority:

Acknowledgment is made of applicants' claim for foreign priority based on an application filed in United Kingdom on 30 June 2003. It is noted, however, that applicant has not filed a certified copy, copy of the 0315291.5 application as required by 35 U.S.C. 119(b). Therefore, benefit of the foreign priority filing dates is not granted. Priority is granted to the date of filing of PCT/EP04/06971, filed 28 June 2004.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 23 December 2005, the 3 April 2006 and the 8 November 2006 have been considered. The signed copies are attached.

Objections

Title:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claims are drawn to an *in vitro* method of determination activation or inactivation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormonal systems.

The following title is suggested: "Methods of determination activation or inactivation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormonal systems.".

Claims:

Claims 2,-16 are objected to because of the following informalities: The claims should be amended to recite "The method according to claim 1..." as only one method is recited in claim 1.

Claim 11 is objected to as failing to further limit claim 3; claim 3 is drawn to a method utilizing an agent comprising SEQ ID NO:1 and SEQ ID NO:6 which are both polypeptides.

Claim 17 is objected to because of the following informalities: the claim would be more grammatically correct if amended to recite, for example, "The method according to claim 1, wherein said method is diagnostic of heart failure or monitors treatment of a cardiac condition."

Claim 22 is objected to as failing to further limit claim 18; claim 18 is drawn to an agent comprising SEQ ID NO:1 and SEQ ID NO:6 which are both polypeptides.

Claims 2, 3, 9, 18, 20, 24, 27, and 38 are objected to as having the incorrect format for sequence identifiers. The claims all have a period after SEQ ID instead of a colon. The claims should be amended to recite SEQ ID NO:X.

Claim 38 is objected to as reciting non-elected inventions. Applicants are required to amend claims to recite only the elected invention, an agent comprising an ANP a BNP.

Claim 38 is drawn to multiple inventions. The claim will be examined to the extent it reads on the elected invention as identified above and in the restriction requirement of 4 June 2008, an agent comprising an NT-proANP (SEQ ID NO:9) and an NT-proBNP (SEQ ID NO:6).

Rejections

35 U.S.C. § 101:

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18, 19, 22-24, and 38 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 18, 19, 22 and 38 are directed to an agent comprising a polypeptide comprising the N-terminal proANP and the N-terminal BNP. The claims, as written do not sufficiently distinguish over a polypeptide that naturally exists in the organism because the claims do not particularly point out any non-naturally occurring differences between the claimed sequences and naturally occurring products.

Claims 23, 24 and 38 are directed to a polynucleotide or an agent comprising a polynucleotide encoding the N-terminal proANP and the N-terminal BNP. The claims, as written do not sufficiently distinguish over a polynucleotide that naturally exists in the organism because the claims do not particularly point out any non-naturally occurring differences between the claimed sequences and naturally

In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. (See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of language indicating an "isolated" polypeptide or polynucleotide (See MPEP 2105).

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, an independent claim of the instant invention, is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential

elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are a statement of how one is to determine if the results of the detection step indicate activation or inactivation of the ANP and BNP hormonal system. One of ordinary skill would be unable to determine, for example, if activation is detected by detecting an increase of the peptide prohormones or a decrease of the peptide prohormones. The claim is also incomplete for failing to specify what the sample is.

Claims 2, 3, 18, 24, 27 and 38 are vague and indefinite in utilizing the same Roman numerals in parts a and b of the claims. For example, in Claims 2, 3, 18 and 38 there are two sections identified as (iii) which refer to sections (i) and (ii). It is unclear if applicants intend the recited fragments to refer to a fragment of NT-proANP or NT-proBNP. In claims 24 and 27 there are two sections identified as (iv) which relate to sections (i), (ii) or (iii). It is unclear if applicants intend the degenerate code of SEQ ID NO:9 or SEQ ID NO:12.

Claims 2, 4, and 38 are vague and indefinite in reciting "an oligospecific ... binding substance" or an "oligospecific antibody". It is unclear if applicant intends to bind an oligonucleotide or an oligopeptide. If applicant intends to bind multiple substances, it is unclear if applicant intends to utilize a substance that binds more than two substances and if so, what those substances might be, since the method is directed to detecting only two substances.

Claims 2, 3, 5, 18, 27 and 38 are vague and indefinite in reciting "homologous sequences". It is unclear what required properties said homologous sequences are to retain.

Claim 3 is vague and indefinite in reciting "an agent comprising" in the 3rd line of the claim and "(c) the agent". It is unclear if applicants intend the method to comprise contacting the sample with one agent or two agents. Furthermore, one of ordinary skill in the art would be unable to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain

natriuretic peptide prohormones that are present in the sample as a result of contacting the sample with an agent comprising atrial and brain natriuretic peptide prohormones as recited in claim 3 (ai) and (bi); thus the claim recites insufficient method steps. Additionally, it is unclear if the first binding substance is to bind an ANP peptide, and a BNP peptide, and an agent (whose characteristics are undisclosed) or bind an agent which comprises ANP and BNP polypeptides.

Claim 7 is vague and indefinite in reciting "an antibody ....or derivative thereof". Since a derivative of an antibody is not defined in the specification, the metes and bounds of "derivative" cannot be determined.

Claim 8 is vague and indefinite in reciting "crossreacting polyclonal antibody. It is unclear what the antibody is to crossreact with.

Claim 10 is vague and indefinite in reciting "the agent". It is unclear which of the agents recited in claim 3 applicant intends to indicate.

Claim 13 is vague and indefinite in reciting "additionally comprises contacting the sample with a second binding substance....". It is unclear at what point in the method of claim 2 the step of contacting recited in Claim 13 is to be performed.

Claim 15 is vague and indefinite in reciting "wherein the second binding substance causes precipitation.....": It is unclear under what conditions applicants intend this precipitation to occur.

Claim 16 is vague and indefinite. It is unclear where in the method of claim 1, the immunoassay is performed. Furthermore, it is unclear what the immunoassay is directed to.

Claim 19 is vague and indefinite. It is unclear if applicants require that there be two sequences present.

It is unclear how the SEQ ID NOs recited in claim 20 are related to the polypeptides recited in claim 19.

Claim 23 is vague and indefinite. Claim 19 does not specify whether the agent comprises two separate proteins or a fusion protein. Thus, it is unclear what "a polypeptide" as recited in Claim 23 refers to.

Claim 24 is vague and indefinite in reciting "a sequence which hybridizes under stringent conditions...". Stringent conditions may be conditions of low, medium or high stringency; thus the term is a relative one within the context ot the claim. Therefore, the metes and bounds of the claim cannot be determined. Additionally, there is no required function recited for the sequences as listed in sections other than section i. Furthermore, the use of Roman numerals in the sections of Claim 24 is confusing. In section (a) of the claim, there are two lines labled as (ii). In section (b) of the claim, there are two lines labeled as (iii). It is unclear which of the sequences "a fragment" refers to, since there are multiple uses of Roman numerals (i) to (v).

The remainder of the claims is included in this rejection as dependent upon rejected claims.

In view of the rejection of claims 2, 3, 18, 24, 27 and 38 under 35 U.S.C. 112, second paragraph and in the interest of compact prosecution, for purposes of prior art, claims 2, 3, 18 and 38 or will be examined to the extent they read on SEQ ID NOs:3 and 6 (the elected species) or a homologous sequence having at least 70% identity to SEQ ID NOs:3 and 6; claims 24 and 27 will be examined to the extent they read on SEQ ID NOs: 9 and 12 (the elected species).

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 21-27 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining activation of the ANP and BNP hormonal system, the method comprising simultaneously detecting the presence or amount of atrial and brain natriuretic peptide prohormones or fragments thereof by contacting the sample with a binding substance that is able to bind to both a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3) or a fragment thereof which is at least 6 amino acids in length and b) (1) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ 1D NO:6) or a fragment thereof which is at least 6 amino acids in length wherein the first binding substance comprises SEQ ID NOs:33 or 34 (Claims 1-17), and for an agent which comprises the identified sequences of SEQ ID NOs 1-6 (claims 18, 21, and 22), a polynucleotide of SEQ ID NOS: 7-12 and a process of producing polypeptides of SEQ ID NOs 1-6 does not reasonably provide enablement for a method comprising contacting the sample with a binding substance that is able to bind to both a homologous sequence having at least 70% identity to a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3) and a homologous sequence having at least 70% identity to b) (1) pro-BNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6) wherein the first binding substance is a sequence having at least 70% identity to SEQ ID NO:33 or a fragment which is at least 70% identical to SEQ ID NO:33 or an agent which comprises a homologous sequence having at least 70% identity to the disclosed sequences (SEQ ID NOs 1-12) or a fragment of any sequence having at least 6 amino acids in length or a sequence which is complementary to or hybridizes to the disclosed nucleotide sequences (SEQ ID NOs 7-12) or a fragment of any of these sequences (SEQ ID NOs 7-12) or a process of producing sequence having at least 70% identity to the disclosed amino acid sequences or fragments thereof which are at least 6 amino acids in length. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).
The claims are broadly drawn to a method comprising contacting the sample with a binding substance that binds to both a homologous sequence which has at least 70% identity to SEQ ID NOs:1-3 and a homologous sequence which has at least 70% identity to SEQ ID NOs:4-6. One of ordinary skill in the art would be unable to practice this method utilizing a binding substance that binds to both a homologous sequence which has at least 70% identity to SEQ ID NOs:1-3 and a homologous sequence which has at least 70% identity to SEQ ID NOs:4-6 since one would be unable to determine, without undue experimentation, which portion of the polypeptide must be retained in order to bind to the recited binding substance. The claims also recite agent comprising sequences which have at least 70% identity to SEQ ID NOs:1-6 and fragments thereof which are at least 6 amino acids in length, polynucleotides which are complementary or hybridise under stringent conditions to SEQ ID NOs 7-12, sequences having 70% identity to sequences of SEQ ID NOs:7-12 and fragments thereof, and methods of producing said polypeptides.

Thus, the claims encompass variant polypeptides and fragments thereof that are encoded by variant polynucleotides and fragments thereof and methods comprising contacting samples with binding substances that bind to said variant polypeptides and fragments thereof. Said binding substances may also comprise variants.

Said variants are not enabled for reasons set forth below.

Variant Polypeptides: The specification teaches polypeptides which are the homologous variants having at least 70% identity to the disclosed sequences

and/or the fragments thereof that comprise at least 6 amino acids in length. [paragraph 0178 of PGPUB 20070141634, the PGPUB of the instant invention]. However, insufficient guidance is presented as to which portions of the polypeptides must be preserved in order to retain the ability to bind to the binding substance as recited in the claims.

Variant Binding substances: The specification teaches that such a binding substance may comprise a receptor or antibody or fragments of either. Additionally, the first binding substance may comprise: (a) natriuretic receptor GC-A (SEQ ID NO: 33), GC-B (SEQ ID NO: 35) or GC-C (SEQ ID NO: 36), homologous variants of said sequences and fragments thereof. The first binding substance may also comprise an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO: 34) or a homologous variant or fragment thereof. [paragraphs 0190-0193]. The claims require that these binding substances, which comprise receptors or the extracellular domains thereof, retain the ability to bind ANP and BNP. However, the disclosure presents insufficient guidance as to which portions of the natriuretic receptor of SEQ ID NO:33 or its extracellular domain must be preserved in order for the required biological activity, binding activity be retained.

Variant Polynucleotides encoding variant agents: These claims are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encompassed by the recitation in the claims encode polypeptides which will retain the characteristics of an ANP and a BNP. While the claims are directed to variant nucleic acids encoding polypeptides, applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible encoded variants of ANP and BNP [paragraphs 0239, 0240, 0253-0257].

The amino acid sequence of the encoded polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from

mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded protein are lacking, it is unpredictable as to which variations, if any meet the limitations of the claims. Applicants are required to enable one of skill in the art to make and use the claimed invention. However, the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed nucleic acids. Since the claims do not enable one of skill in the art to make and use the claimed nucleic acids, but only teaches how to screen for the claimed nucleic acids, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. It would require undue experimentation of one of skill in the art to make and use the claimed invention.

Example 1 teaches nucleotides encoding amino acids 1-37 of human NT-proBNP and amino acids 29-98 of human NT-proANP. There are no examples, working or prophetic of nucleotides complementary or which hybridize to those described above, or sequences that are 70% homologous to said nucleotide sequences, or fragments thereof. The working examples are also directed to generation of antibodies (binding substances) using a fusion protein comprising NT-pro-BNP 1-37 and NT-proANP 29-98 and measuring the plasma levels of NT-proANP and NT-pro BNP in patients suffering heart failure (Example 3). There are no examples, working or prophetic, directed to assays which measure the binding of substances to polypeptide sequences having at least 70% identity to the proteins of interest, binding assays utilizing binding substances which have 70% identity to SEQ ID NO:33 or are fragments of SEQ ID NO:33 which are at least 400 amino acids in length

Due to the large quantity of experimentation necessary to determine whether the recited binding substance comprising variant sequences or fragments will bind to polypeptide sequences having 70% identity to the

disclosed sequences (SEQ ID NOs 1-6), and whether variant nucleic acids will encode functional peptides, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite which portions of the homologous sequences will be retain the required binding characteristics and which homologous sequences would be able to bind to the binding substances, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims **1-18, 21-27 and 38** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to assays utilizing homologous sequences having at least 70% identity to SEQ ID NOs 1-6 or fragments thereof, nucleic acids encoding said sequences which are complementary to or hybridize to nucleic acids of SEQ ID NOs 7-12 or variants having at least 70% sequence identity with SEQ ID NOs:7-12 or fragments thereof and agents comprising said polypeptides or polynucleotides. The claims are also drawn to binding substances comprising homologous sequences having at least 70% identity to SEQ ID NO:33 and fragments thereof which are at least 400 amino acids in length. The claims do not require that the polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The claims do not require that the nucleic acids encode functional polypeptides. Thus, the claims are drawn to several genera: a genus of nucleic acids that is defined only by sequence identity or hybridization ability, and genera of polypeptides identified only by sequence identity.

To provide evidence of possession of the claimed genera, the specification must provide sufficient distinguishing identifying characteristics of the genera. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or hybridization ability. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polypeptides comprising the amino acid sequences of SEQ ID NOs 1-6, polynucleotides comprising SEQ ID NOs:7-12 and binding substances comprising SEQ ID NOs:33 and 34 and methods utilizing said sequences, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998. J Endoc. Invest 21:170-179, cited on IDS of 3 April 2006, reference 2 on page 2) in view of Clerico et al. (2000. Clin. Chemistry 46:1529-1534). The claims are drawn to an in vitro method comprising simultaneously detecting the presence or amount of atrial and brain

natriuretic peptide prohormones (proANP and proBNP) in a sample wherein the method comprises an immunoassay, thereby diagnosing heart failure or monitoring treatment of a cardiac condition.

Clerico et al (1998) teach measurement of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in plasma of patients with heart failure as an assay method useful in follow-up of cardiac patients (monitoring a cardiac condition) (abstract). The measurements are performed on plasma samples from healthy subjects and patients with chronic cardiomyopathy (page 172, 1st column, 2nd paragraph). The polypeptides were both measured in samples from the same subject (page 174, 1st column, 3rd paragraph and page 175, 2nd column, last paragraph); absent evidence to the contrary, said measurements would constitute simultaneous detection. The measurements were performed using non-competitive immunoradiometric assays (IRMA) (page 172, 1st column, last paragraph bridging page 173, 2nd column, 1st paragraph). Clerico et al (1998) does not teach a method comprising detecting the presence of atrial and brain natriuretic peptide prohormones or fragments thereof. Clerico et al (2000) teach that cardiac natriuretic hormones are a family of related peptides including ANP, BNP and other peptides derived from the N-terminal portion of proANP and proBNP peptide chains (abstract). The reference teaches that the N-terminal prohormones are present in greater amounts in the plasma than ANP and BNP (Table 1) .

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and substitute measurement of proANP and proBNP (as taught by Clerico et al (2000)) for the measurement of ANP and BNP as taught by Clerico et al. (1998). The person of ordinary skill in the art would have been motivated to make these modifications because Clerico et al (2000) teach that the prohormones are present in higher concentrations in the plasma and one of ordinary skill in the art would recognize that these may be measured more easily and accurately. One

would reasonably have expected success because methods of measuring said prohormones are outlined by Clerico et al (2000).

With respect to claims 3, 4 and 9-11, as noted above, the claims are vague and indefinite. However, in reviewing the claims in light of the teachings in the specification, ("an agent may be used as a standard to calibrate the present assays. The agent may be used as a competing antigen in a competition assay [paragraph 0134]") the Examiner has interpreted these claims to be directed to a competitive binding assay, such as a radioimmunoassay.

Claims 2-4, 7, and 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) as applied to claim 1 further in view of Buechler et al (US 7,341,838, filed 19 April 2004, priority claimed to provisional application 60/466,358, filed 28 April 2003, the '838 patent). The teachings of Clerico et al (1998) and Clerico et al (2000) are outlined in detail above. In addition to the teachings above, Clerico et al. (2000) teach competitive assays such as radioimmunoasssays comprising labeled antigens such as ANP and BNP (abstract). The references, singly or in combination, do not teach the further limitations of contacting the sample with a bi- or oligo-specific binding substance that is able to bind to both NT-proANP of SEQ ID NO:3 and NT-proBNP of SEQ ID NO:6 (Claim 2) wherein the binding substance comprises an antibody that binds to NT-proANP of SEQ ID NO:3 and NT-proBNP (SEQ ID NO:6) (Claims 7 and 8), wherein the first binding substance or agent is labeled and/or immobilized (claim 12) and a method which additionally comprises contacting the sample with a second binding substance which is able to bind to the first binding substance, wherein the second binding substance is labeled or immobilized and wherein a precipitate is formed (claims 13-15).

The '838 patent teaches a sequence (SEQ ID NO:3) comprising a segment, amino acids 1-98, which is 99.4% identical to SEQ ID NO:3 of the instant invention (see alignment below and results in SCORE). SEQ ID NO:3 of the '838 patent is identified as an ANP precursor, pro-ANP (pro-hormone)

Alignment match for SEQ ID NO:3 of the instant invention

```
  Query Match             99.4%;  Score 509;  DB 3;  Length 126;
  Best Local Similarity   99.0%;  Pred. No. 4.6e-52;
  Matches   97;  Conservative    1;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 60
              |||||||||||||||||||||||||||||||||||||||||:||||||||||||||||||
Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
              ||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPR 98
```

The reference also teaches a sequence, SEQ ID NO:1, comprising a segment, amino acids 1-76 which is 100% identical to SEQ ID NO:6 of the instant invention (see alignment below and results in SCORE). SEQ ID NO:1 is identified as a BNP-precursor molecule (pro-hormone) (column 12, lines 49-55)

Alignment match for SEQ ID NO:6 of the instant invention

```
  Query Match             100.0%;  Score 392;  DB 3;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 4.1e-41;
  Matches   76;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPR 76
              ||||||||||||||||
Db         61 IRGHRKMVLYTLRAPR 76
```

One of ordinary skill in the art would recognize that antibodies which recognize polypeptides comprising segments 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively, of the instant invention would recognize the polypeptides of the instant invention. The '838 patent teaches measuring

fragments in samples; said fragments could be pro-ANP and pro-BNP (column 15, lines 36-43). The fragments are recognized by antibodies. Said antibodies may comprise bivalent antibodies, comprising two Fab fragments linked by a disulfide bridge at the hinge region (column 16, lines 21-23), thus teaching a bispecific binding substance that binds to proANP and proBNP, as required by claims 2 and 7. The antibodies may be monoclonal antibodies or polyclonal antibodies (column 16, lines 34-39), as required by claim 8. The reference teaches immunoassays comprising a tagged antibody (column 18, lines 24-26), a limitation of claim 12. The '838 patent teaches immunoassays comprising labeled antimmunoglobulin antibodies (column 18 lines 53-55), thus meeting the limitations of claims 13 and 14. The reference also teaches "capture" or "sandwich" ELISA wherein the antigent-antibody-2nd antibody complex precipitates (column 18, line 60 bridging column 19, line 3) and radioimmunassays (column 18, lines 32-55).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and Clerico et al (2000) and substitute the polypeptides of SEQ ID NOs: 3 and 1 as taught by the '838 patent for the generic proANP and pro-BNP taught by the Clerico et al (2000) and utilize the antibodies and immunoassays taught by the '838 patent in place of the IRMA assays taught by Clerico et al (1998). The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP and one of skill in the art would recognize that one may use bivalent antibodies to bind to different antigens and that different types of immunoassays (RIAs, IRMAs and ELISAs) are art-recognized equivalents. One would reasonably have expected success because methods of making bivalent antibodies for use in diverse immunoassays and methods of practicing different immunoassays are well known in the art.

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998) in view of Clerico et al. (2000) and Buechler et al (the '838 patent) as applied to Claims 1 and 2 and further in view of Bentivegna et al. (WO 01/79231, the '231 reference). The teachings of Clerico et al (1998), Clerico et al (2000), and the '838 patent are outlined in detail above. The references, singly or combined, do not teach the further limitations of a method wherein the binding substance comprises the natriuretic receptor GC-A (SEQ ID NO:33) or comprises an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO:34). The '231 reference teaches a sequence, SEQ ID NO:3, which is 100% identical to SEQ ID NO:33 of the instant invention (See alignment below and results in SCORE). This sequence comprises a domain, the extracellular ligand binding domain, that is 100% identical to SEQ ID NO:34 of the instant invention (See alignment below and results in SCORE). The reference identifies the sequence as the human NPR1 (receptor) polypeptide.

Alignment match for SEQ ID NO:33 of the instant invention

```
   Sequence 1061 AA;

  Query Match             100.0%;  Score 5543;  DB 5;  Length 1061;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 1061;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MPGPRRPAGSRLRLLLLLLLPLLLLLRGSHAGNLTVAVVLPLANTSYPWSWARVGPAVE 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MPGPRRPAGSRLRLLLLLLLPLLLLLRGSHAGNLTVAVVLPLANTSYPWSWARVGPAVE 60

Qy         61 LALAQVKARPDLLPGWTVRTVLGSSENALGVCSDTAAPLAAVDLKWEHNPAVFLGPGCVY 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 LALAQVKARPDLLPGWTVRTVLGSSENALGVCSDTAAPLAAVDLKWEHNPAVFLGPGCVY 120

Qy        121 AAAPVGRFTAHWRVPLLTAGAPALGFGVKDEYALTTRAGPSYAKLGDFVAALHRRLGWER 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 AAAPVGRFTAHWRVPLLTAGAPALGFGVKDEYALTTRAGPSYAKLGDFVAALHRRLGWER 180

Qy        181 QALMLYAYRPGDEEHCFFLVEGLFMRVRDRLNITVDHLEFAEDDLSHYTRLLRTMPRKGR 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 QALMLYAYRPGDEEHCFFLVEGLFMRVRDRLNITVDHLEFAEDDLSHYTRLLRTMPRKGR 240

Qy        241 VIYICSSPDAFRTLMLLALEAGLCGEDYVFFHLDIFGQSLQGGQGPAPRRPWERGDGQDV 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VIYICSSPDAFRTLMLLALEAGLCGEDYVFFHLDIFGQSLQGGQGPAPRRPWERGDGQDV 300

Qy        301 SARQAFQAAKIITYKDPDNPEYLEFLKQLKHLAYEQFNFTMEDGLVNTIPASFHDGLLLY 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        301 SARQAFQAAKIITYKDPDNPEYLEFLKQLKHLAYEQFNFTMEDGLVNTIPASFHDGLLLY 360

Qy        361 IQAVTETLAHGGTVTDGENITQRMWNRSFQGVTGYLKIDSSGDRETDFSLWDMDPENGAF 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 IQAVTETLAHGGTVTDGENITQRMWNRSFQGVTGYLKIDSSGDRETDFSLWDMDPENGAF 420

Qy        421 RVVLNYNGTSQELVAVSGRKLNWPLGYPPPDIPKCGFDNEDPACNQDHLSTLEVLALVGS 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 RVVLNYNGTSQELVAVSGRKLNWPLGYPPPDIPKCGFDNEDPACNQDHLSTLEVLALVGS 480

Qy        481 LSLLGILIVSFFIYRKMQLEKELASELWRVRWEDVEPSSLERHLRSAGSRLTLSGRGSNY 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 LSLLGILIVSFFIYRKMQLEKELASELWRVRWEDVEPSSLERHLRSAGSRLTLSGRGSNY 540

Qy        541 GSLLTTEGQFQVFAKTAYYKGNLVAVKRVNRKRIELTRKVLFELKHMRDVQNEHLTRFVG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 GSLLTTEGQFQVFAKTAYYKGNLVAVKRVNRKRIELTRKVLFELKHMRDVQNEHLTRFVG 600

Qy        601 ACTDPPNICILTEYCPRGSLQDILENESITLDWMFRYSLTNDIVKGMLFLHNGAICSHGN 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 ACTDPPNICILTEYCPRGSLQDILENESITLDWMFRYSLTNDIVKGMLFLHNGAICSHGN 660

Qy        661 LKSSNCVVDGRFVLKITDYGLESFRDLDPEQGHTVYAKKLWTAPELLRMASPFVRGSQAG 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 LKSSNCVVDGRFVLKITDYGLESFRDLDPEQGHTVYAKKLWTAPELLRMASPFVRGSQAG 720

Qy        721 DVYSFGIILQEIALRSGVFHVEGLDLSPKEIIERVTRGEQPPFRPSLALQSHLEELGLLM 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 DVYSFGIILQEIALRSGVFHVEGLDLSPKEIIERVTRGEQPPFRPSLALQSHLEELGLLM 780

Qy        781 QRCWAEDPQERPPFQQIRLTLRKFNRENSSNILDNLLSRMEQYANNLEELVEERTQAYLE 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 QRCWAEDPQERPPFQQIRLTLRKFNRENSSNILDNLLSRMEQYANNLEELVEERTQAYLE 840

Qy        841 EKRKAEALLYQILPHSVAEQLKRGETVQAEAFDSVTIYFSDIVGFTALSAESTPMQVVTL 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 EKRKAEALLYQILPHSVAEQLKRGETVQAEAFDSVTIYFSDIVGFTALSAESTPMQVVTL 900

Qy        901 LNDLYTCFDAVIDNFDVYKVETIGDAYMVVSGLPVRNGRLHACEVARMALALLDAVRSFR 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 LNDLYTCFDAVIDNFDVYKVETIGDAYMVVSGLPVRNGRLHACEVARMALALLDAVRSFR 960

Qy        961 IRHRPQEQLRLRIGIHTGPVCAGVVGLKMPRYCLFGDTVNTASRMESNGEALKIHLSSET 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 IRHRPQEQLRLRIGIHTGPVCAGVVGLKMPRYCLFGDTVNTASRMESNGEALKIHLSSET 1020

Qy       1021 KAVLEEFGGFELELRGDVEMKGKGKVRTYWLLGERGSSTRG 1061
              |||||||||||||||||||||||||||||||||||||||||
Db       1021 KAVLEEFGGFELELRGDVEMKGKGKVRTYWLLGERGSSTRG 1061
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Alignment match for SEQ ID NO:34 of the instant invention

```
  Query Match           100.0%;  Score 2303;  DB 5;  Length 1061;
  Best Local Similarity  100.0%;  Pred. No. 3.2e-201;
  Matches  430;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GNLTVAVVLPLANTSYPWSWARVGPAVELALAQVKARPDLLPGWTVRTVLGSSENALGVC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         33 GNLTVAVVLPLANTSYPWSWARVGPAVELALAQVKARPDLLPGWTVRTVLGSSENALGVC 92

Qy         61 SDTAAPLAAVDLKWEHNPAVFLGPGCVYAAAPVGRFTAHWRVPLLTAGAPALGFGVKDEY 120
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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          93 SDTAAPLAAVDLKWEHNPAVFLGPGCVYAAAPVGRFTAHWRVPLLTAGAPALGFGVKDEY 152

Qy         121 ALTTRAGPSYAKLGDFVAALHRRLGWERQALMLYAYRPGDEEHCFFLVEGLFMRVRDRLN 180
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         153 ALTTRAGPSYAKLGDFVAALHRRLGWERQALMLYAYRPGDEEHCFFLVEGLFMRVRDRLN 212

Qy         181 ITVDHLEFAEDDLSHYTRLLRTMPRKGRVIYICSSPDAFRTLMLLALEAGLCGEDYVFFH 240
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         213 ITVDHLEFAEDDLSHYTRLLRTMPRKGRVIYICSSPDAFRTLMLLALEAGLCGEDYVFFH 272

Qy         241 LDIFGQSLQGGQGPAPRRPWERGDGQDVSARQAFQAAKIITYKDPDNPEYLEFLKQLKHL 300
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         273 LDIFGQSLQGGQGPAPRRPWERGDGQDVSARQAFQAAKIITYKDPDNPEYLEFLKQLKHL 332

Qy         301 AYEQFNFTMEDGLVNTIPASFHDGLLLYIQAVTETLAHGGTVTDGENITQRMWNRSFQGV 360
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         333 AYEQFNFTMEDGLVNTIPASFHDGLLLYIQAVTETLAHGGTVTDGENITQRMWNRSFQGV 392

Qy         361 TGYLKIDSSGDRETDFSLWDMDPENGAFRVVLNYNGTSQELVAVSGRKLNWPLGYPPPDI 420
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         393 TGYLKIDSSGDRETDFSLWDMDPENGAFRVVLNYNGTSQELVAVSGRKLNWPLGYPPPDI 452

Qy         421 PKCGFDNEDP 430
                ||||||||||
Db         453 PKCGFDNEDP 462
```

The art teaches (See, for teaching purposes only, Tremblay et al 2002. Mol and Cell Biochem. 230:31-47, abstract and Figure 1) that the NPR1 receptor (also known as the natriuretic receptor or NPR-A) comprises an extracellular natriuretic peptide-binding domain which binds both ANP and BNP.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) Clerico et al (2000) and the '838 patent and substitute the receptor taught by the '231 reference, which binds both BNP and ANP for the antibodies which bind BNP and ANP (taught by Clerico et al (1998) Clerico et al (2000) and the '838 patent) in the methods of the instant invention. The person of ordinary skill in the art would have been motivated to make these modifications and reasonably have expected success because one of ordinary skill in the art would recognize that both receptors comprising extracellular ligand binding domains and antibodies may be used to bind antigens such as ANP and BNP and would be aware that the NPR1 receptor binds both ANP and BNP.

Claims 18- 22 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakata et al. (2001. EP1 118 329 A1, cited on ID of 3 April 2006, page 1, reference 4 of Foreign Patents) in view of Buechler et al (the '838 patent). Nakata et al teach eye drops comprising compositions comprising natriuretic peptides including ANP and BNP; ANP and BNP having different structure (prohormones, fragments) are known and the natriuretic peptides in compositions taught by Nakata et al include all of them [paragraph 0010]. Thus, the compositions taught by Nakata et al. encompass an agent comprising ANP and BNP, prohormones and fragments thereof. Nakata et al do not teach agents comprising a sequence having at least 70% identity to SEQ ID NO:3 (NT-proANP) and a NT-proBNP of SEQ ID NO:6 or an agent comprising proBNP1-108 and proANP1-126 which comprises SEQ ID NO:19. As stated above, the '838 patent teaches polypeptides which comprise sequences comprising segments that are 99.4% and 100% identical to SEQ ID NO:3 and SEQ ID NO:6, respectively. The '838 patent also teaches sequences comprising proBNP1-108 (SEQ ID NO:1 disclosed in the '838 patent) and a proANP1-126 (SEQ ID NO:3 disclosed in the '838 patent).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Nakata et al. and substitute the polypeptides comprising segments of SEQ ID NOs: 3 and 1 or sequences comprising proBNP1-108 and proANP1-126 as taught by the '838 patent for the generic ANP and BNP and ANP and BNP peptides having different structures as taught by Nakata et al. The person of ordinary skill in the art would have been motivated to make these modifications because the '838 patent identifies the polypeptides of SEQ ID NOs:3 and 1 as proANP and pro-BNP. Additionally, it would be obvious to one of skill in art to make a fusion protein comprising proBNP1-108 and proANP1-126 comprising SEQ ID NO: 1 and SEQ ID NO:3 taught by the '858 protein to arrive at a fusion protein of SEQ ID NO:19 of the instant invention, which comprises as amino acids 1-108 a sequence which is 100% identical to SEQ ID NO:1 of the referenced patent and as amino

acids 109-234 a sequence which is 99.2% identical to SEQ ID NO:3 of the referenced patent (See alignment below and results in SCORE. The one amino acid difference comprises the conservative substitution of aspartic acid for glutamic acid (both being acidic amino acids; one of skill in the art would predict that this would not change the biological activity of the the fusion protein. One would be motivated to make said fusion protein so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies (as disclosed by the '838 patent) to detect both proteins. One would have a reasonable expectation of success because methods of making fusion proteins are well known in the art.

Alignment match for amino acids 1-108 of SEQ ID NO:19 of the instant invention

```
  Query Match             45.9%;  Score 561;  DB 3;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 3.6e-49;
  Matches  108;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 HPLGSPGSASDLETSGLQEQRNHLQGKLSELQVEQTSLEPLQESPRPTGVWKSREVATEG 60

Qy         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
              ||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 IRGHRKMVLYTLRAPRSPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH 108
```

Alignment match for amino acids 109-234 of SEQ ID NO:19 of the instant invention

```
  Query Match             53.9%;  Score 659;  DB 3;  Length 126;
  Best Local Similarity   99.2%;  Pred. No. 4.6e-59;
  Matches  125;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        109 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSEPNEEAGAALSPLPEVPPWTG 168
              |||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
Db          1 NPMYNAVSNADLMDFKNLLDHLEEKMPLEDEVVPPQVLSDPNEEAGAALSPLPEVPPWTG 60

Qy        169 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 228
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 EVSPAQRDGGALGRGPWDSSDRSALLKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLG 120

Qy        229 CNSFRY 234
              ||||||
Db        121 CNSFRY 126
```

Claims 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewicki et al (US 5,212,286, the '286 patent) and Simari (WO 00/71576, the '576 reference).

The '286 patent teaches a sequence, SEQ ID NO:3, comprising a sequence that is 100% identical to SEQ ID NO:9 of the instant invention (See alignment below and results in SCORE). The '286 patent teaches this nucleotide sequence as encoding an atrial natriuretic peptide. The reference teaches expression vectors (for example, column 6, lines 3-18, column 71, line 25) host cells (column 82, lines 46-54), and methods of making the protein of interest recombinantly (column 13, lines 38-42, and column 82, lines 46-54).

Alignment match for SEQ ID NO:9 of the instant invention

```
  Query Match             100.0%;  Score 294;  DB 2;  Length 702;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-86;
  Matches  294;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         32 AATCCCATGTACAATGCCGTGTCCAACGCAGACCTGATGGATTTCAAGAATTTGCTGGAC 91

Qy         61 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         92 CATTTGGAAGAAAAGATGCCTTTAGAAGATGAGGTCGTGCCCCCACAAGTGCTCAGTGAG 151

Qy        121 CCGAATGAAGAAGCGGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        152 CCGAATGAAGAAGCGGGGGCTGCTCTCAGCCCCCTCCCTGAGGTGCCTCCCTGGACCGGG 211

Qy        181 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        212 GAAGTCAGCCCAGCCCAGAGAGATGGAGGTGCCCTCGGGCGGGGCCCCTGGGACTCCTCT 271

Qy        241 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 294
              ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        272 GATCGATCTGCCCTCCTAAAAAGCAAGCTGAGGGCGCTGCTCACTGCCCCTCGG 325
```

The '576 reference teaches a sequence comprising a sequence that is 100% identical to SEQ ID NO:12 of the instant invention (See alignment below and results in SCORE). This sequence is described as encoding a natriuretic

peptide, BNP, useful to inhibit or prevent heart failure. The reference teaches plasmids (page 7, 5th paragraph, Figure 3) and host cells expressing the protein of interest and methods of isolating recombinantly produced protein (page 7, 6th paragraph, Figure 4)

Alignment match for SEQ ID NO:12 of the instant invention

```
  Query Match             100.0%;  Score 228;  DB 4;  Length 330;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-49;
  Matches  228;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          4 CACCCGCTGGGCAGCCCCGGTTCAGCCTCGGACTTGGAAACGTCCGGGTTACAGGAGCAG 63

Qy         61 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         64 CGCAACCATTTGCAGGGCAAACTGTCGGAGCTGCAGGTGGAGCAGACATCCCTGGAGCCC 123

Qy        121 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        124 CTCCAGGAGAGCCCCCGTCCCACAGGTGTCTGGAAGTCCCGGGAGGTAGCCACCGAGGGC 183

Qy        181 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 228
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db        184 ATCCGTGGGCACCGCAAAATGGTCCTCTACACCCTGCGGGCACCACGA 231
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In addition to the teachings above, the '286 patent teaches that compounds of the disclosed invention (polypeptides encoded by the disclosed nucleotide sequences) may be mixed with, bonded to or conjugated with compounds having the same or a complementary range of biological activities. One of skill in the art would recognize that both ANP and BNP have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects (See, for teaching purposes only, Clerico et al (2000), cited above).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of the '286 patent and the '576 reference to produce a composition comprising the nucleotides disclosed in each of the references. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because the '286 patent teaches that compounds of the disclosed invention (polypeptides encoded

by the disclosed nucleotide sequences) may be mixed with, bonded to or conjugated with compounds having the same or a complementary range of biological activities, and thus it would be advantageous to have a composition comprising polynucleotides encoding both ANP and BNP in order to efficiently produce said polypeptides recombinantly, since the art teaches both polypeptides have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Lorraine Spector/ Ph.D.
Primary Examiner, Art Unit 1647

/S. H. S./
Examiner, Art Unit 1647